

## **REMARKS**

### **In the Specification:**

The Examiner objected to the disclosure because it contains embedded hyperlinks and/or other forms of browser-executable code. The Examiner has stated that under MPEP § 608.01, Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. Per the Examiner's request, and in compliance with MPEP § 608.01, Applicant has deleted the embedded hyperlinks and/or other forms of browser-executable code. Therefore, Applicant respectfully requests that this ground of objection be withdrawn.

The Examiner also objected to the disclosure, alleging that the tables are not labeled consecutively. Specifically, the Examiner contends that the first table is Table 6 on page 61. Applicant respectfully disagrees and directs the Examiner's attention to Table 1, beginning on page 34 and running through page 50 of the instant application. Table 2 appears on page 51, Table 3 on page 52, Table 4 on page 53, and Table 5 on page 54. Therefore, Applicant submits that Table 6, on page 61, as well as the tables that follow Table 6, are consecutively labeled and Applicant respectfully requests that the Examiner withdraw this ground of objection.

### **In the Claims:**

Claim 22 has been amended to clarify that the claimed antibody is an isolated antibody that specifically binds to the polypeptide of SEQ ID NO:50. Support for amendment to Claim 22 may be found at pages 16, 82, 88, and 116 of the specification. Claim 25 has been amended to clarify that what is claimed is an isolated antibody fragment. Support for amendment to Claim 25 may be found in original Claim 25, as well as pages 32 and 33 of the specification.

**Claim Rejections:**

**35 U.S.C. § 101**

Claims 22 and 27 are rejected under 35 U.S.C. 101 as being directed to non-statutory subject matter. Claim 22 has been amended to clarify that the claimed antibody is an isolated antibody, as suggested by the Examiner. Claim 27 has been canceled. Therefore, this ground of rejection has been overcome and Applicant respectfully requests withdrawal of this ground of rejection.

The Examiner has rejected claims 22-27 under 35 U.S.C. 101 because allegedly the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The Examiner contends that the instant specification does not describe any biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner or any other specific feature that is associated with PRO347. Applicant respectfully disagrees. Applicant submits that several structural features, such as open reading frames, translation initiation sites, molecular weight and pI of the cDNA sequence of PRO347 are disclosed at lines 21-26 on page 103. At page 142, line 19, the specification discloses tissues where PRO347 nucleic acids are significantly expressed and where they are not.

Further, as the Examiner notes, the results of gene amplification experiments, which measure  $\Delta C_t$  values for PRO347 (one  $\Delta C_t$  unit is defined as corresponding to 1 PCR cycle or approximately a 2-fold amplification relative to normal), are presented in Table 10 on page 127. However, according to the Examiner, this table does not identify which columns of  $\Delta C_t$  values correspond to PRO347. Applicant respectfully disagrees. Specifically, at line 3 on page 127, each column is identified as corresponding to a particular PRO. More specifically, the fourth column from the right side of page 127 sets forth the  $\Delta C_t$  values, 1.315 and 1.525, for PRO347 in human colon tumor samples. Thus Applicant submits that the data demonstrates amplification of the PRO347 gene in primary tumors.

In fact, the Examiner noted that the specification discloses that nucleic acids encoding PRO347 have a  $\Delta C_t$  value of at least 1.0 for a number of primary lung and colon tumors and/or cell lines. However, the Examiner contends that it is not clear what the significance of such a  $\Delta C_t$  value would be. Applicant submits that this data (the  $\Delta C_t$  values) supports a diagnostic utility for nucleic acids, polypeptides and antibodies to PRO347 and respectfully directs the attention of the Examiner to the declaration of Audrey D. Goddard, Ph.D., attached hereto as Appendix A ("the Goddard Declaration"). The Goddard Declaration makes it clear that skilled artisans recognize a well-established utility for the claimed invention at the time of filing.

Specifically, the Goddard Declaration illustrates the acceptance in the art of gene amplification data as an indicator of cancerous tissue. For example, in paragraph 7, Dr. Goddard specifically asserts her opinion that:

[a]n at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number . . . as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology.

Goddard Declaration, paragraph 7.

The pending claims are directed to antibodies against proteins encoded by one of the amplified DNA sequences. The specification specifically asserts a utility for these antibodies. See, for example, page 137, lines 22-24, stating that "[a]ntagonists (e.g., antibodies) directed against the proteins encoded by the DNAs tested would be expected to have utility in cancer therapy and as useful diagnostic reagents."

The Examiner indicated that the significance of a difference of 1 or 2 PCR cycles is not clear. The specification indicates that one  $\Delta C_t$  unit corresponds to 1 PCR cycle, or *approximately a 2-fold amplification relative to normal* (see page 120, lines 7-9). Furthermore, as indicated above, the Goddard Declaration indicates that a 2-fold increase in gene copy number is considered both significant and useful (see Goddard

Declaration paragraph 7, and above). Thus, the  $\Delta$  Ct data is indicative of relevant gene amplification.

The Examiner further indicates that, even if the data demonstrates a slight increase in copy number of PRO347 nucleic acids in primary tumors, such increase would not be indicative of a use of the encoded polypeptide as a diagnostic agent because cancerous tissue is known to be aneuploid. The Examiner asserts that the data presented in the specification were not corrected for aneuploidy, and that a slight amplification of a gene does not necessarily mean over expression in a cancer tissue, but can merely be an indication that the tissue is aneuploid.

Applicant respectfully disagrees with this characterization. The data presented in the specification are from experiments using appropriate controls for aneuploidy (see, for example, page 137, lines 13-16). Applicant used framework mapping to control for aneuploidy and to ensure that the observed  $\Delta$ Ct data represent relevant gene amplification. Thus, the reported data are an indication of relevant gene amplification, and support the conclusion that PRO347, and related proteins and antibodies, can be used as a cancer diagnostic. Furthermore, considering the aneuploidy controls used by the Applicant, a skilled artisan would not be required to undertake undue experimentation to practice the claimed invention.

The Examiner further argues that an increase in the mRNA level expression does not necessarily result in increased protein expression levels. Applicant respectfully directs the Examiner's attention to several publications and abstracts of publications that demonstrate that mRNA levels correlate with protein expression levels, attached hereto as Appendix B. These publications make it clear that skilled artisans recognize that the expression levels of mRNA often correlate with the protein expression levels. For example, Maruyama *et al.* (Am. J. of Pathol., Sept. 1999, Vol. 155, No. 3, pgs. 815-822) showed a correlation between mRNA levels and protein levels of three of the helix-loop-helix proteins, Id-1, Id-2, and Id-3. According to Maruyama *et al.*, the mRNA and protein levels of all three species were increased in pancreatic cancer tissues as compared to the normal or chronic pancreatitis control tissues. Also, Ginestier *et al.* (Am. J. Pathol., Oct. 2002, 161(4):1223-

33) demonstrated a correlation between cDNA (cDNA array analysis) and protein expression levels (using tumor tissue microarray analysis) in one-third of the examined molecules with proven or suspected role in breast cancer.

Applicant also includes several other publications for the Examiner's consideration. For example, Dalifard *et al.* (Int. J. Mol. Med., May 1998, 1(5):855-61) showed that in breast cancer, a correlation ( $r=0.85$ ) existed between c-erbB2 (oncogene encoding for p185 protein) expression (as determined by Southern blot method) and p185 protein expression levels (as determined by immunoenzymetric assay). Also, Hareuveni *et al.* (Eur. J. Biochem., May 1990, 189(3): 475-86) found a correlation between expressed tumor antigen species with the allelic forms as well as significantly increased protein expression in breast cancer. Furthermore, Barr *et al.* (J. Parasitol., April 2003, 89(2):381-4) demonstrated that in a canine model of Chagas disease, mRNA levels (as determined by Northern blotting) and protein expression levels (as determined by Western blotting) of the plasma membrane calcium pump (PMCA) were increased in cardiac tissue by 77% and 58%, respectively, as compared to normal controls.

Accordingly, because the RNA levels and the protein expression levels have been found to correlate in different types of cancers as well as other diseases, Applicant asserts that it is reasonable to expect the protein levels of the polypeptide encoded by the SEQ ID NO: 50 to be increased in cancer tissue.

In view of these remarks, Applicant respectfully asserts that the claimed invention has utility and is fully enabled. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejections under § 101.

### **35 U.S.C. § 112, first paragraph**

Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement based on the Examiner's finding that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicant submits that as explained above, claims 22-27 are supported by both a specific and substantial

utility and a well established utility. Therefore, this ground of rejection has been overcome and Applicant respectfully requests that it be withdrawn.

### **35 U.S.C. § 112, second paragraph**

The Examiner has rejected Claim 25 as indefinite because according to the Examiner, an antibody cannot be both an antibody and an antibody fragment. Applicant has amended Claim 25 to clarify that it encompasses an isolated antibody fragment that specifically binds the polypeptide of SEQ ID NO:50. Therefore, this ground of rejection has been overcome and Applicant respectfully requests that it be withdrawn.

The Examiner has also rejected Claim 27, alleging that the term "specifically" binds is unclear. Applicant has cancelled Claim 27 and therefore respectfully requests the rejection be withdrawn.

However, Applicant has amended Claim 22 to recite "specifically" binds. Applicant submits that the phrase "specifically binds" has a well-understood meaning in the art and that in light of this well understood meaning that is consistent with how that phrase is used on pages 16, 82, 88, and 116, as well as in the claims of the instant application.

### **Priority Determination**

The Examiner, based on her finding of lack of utility and enablement, alleges that the effective priority date for this application is 8/30/01. Applicant respectfully traverses this determination for at least the following reasons. Applicant has claimed priority to U.S. Application Serial No. 60/113,296, filed 12/22/1998, which discloses PRO347 (see Figure 14, SEQ ID NO: 14 and pages 50-51 of 60/113,296), as well as several specific, substantial and credible utilities for the claimed antibodies that bind PRO347.

For example, 60/113,296 discusses using the claimed invention (1) as an antagonist or agonist of PRO347 at lines 14-17 on page 3, (2) for determining the presence of PRO347 at lines 26-32 on page 3, (3) for diagnosing a tumor by detecting the level of expression of a gene encoding PRO347 at lines 33-35 on page 3 - lines 1-24 on page 4,

(4) for inhibiting the growth of tumor cells at lines 25-35 on page 4 - lines 1-21 on page 5. Further, at pages 23-28, 60/113,296 discusses detecting gene amplification/expression of PRO347 in certain tissues and at pages 28-29, 60/113,296 describes anti-PRO347 antibody binding studies.

Moreover, at pages 55-101, 60/113,296 describes methods for determining whether the genes encoding various PRO polypeptides are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. As with U.S. Application Serial No. 09/944,449, the gene amplification examples measure and discuss  $\Delta$  Ct values. Further, the Goddard Declaration, discussed above, demonstrates that the skilled artisan would understand the significance of the  $\Delta$  Ct value data discussed in the gene amplification studies.

Table 2, found at pages 65-72 sets forth the  $\Delta$  Ct values for various PRO polypeptides in various tissues. The  $\Delta$  Ct values for PRO347 are listed in the 8th column from the top, left-hand side of the page. This data demonstrates that the PRO347 gene is amplified in cancerous tissues. The results of the gene amplification study with respect to PRO347 are discussed at page 105, lines 22-33. Amplification of PRO347 DNA was detected in various tumors and therefore, as stated at page 105, lines 32-33, "antagonists, (e.g. antibodies) directed against the protein encoded by DNA44176 (PRO347) would be expected to be useful in cancer therapy."

For at least these reasons, Applicant submits that U.S. Application Serial No. 60/113,296 discloses specific, substantial and credible utilities for the claimed antibodies that bind PRO347. Applicant respectfully asserts that the proper priority date for the claimed invention is 12/22/1998, and requests that the Examiner reconsider the determination of priority.

### **35 U.S.C. § 102**

The Examiner rejected claim 25 under 35 U.S.C. 102(b) as being anticipated by Immunobiology (Third Ed.) because the Examiner alleges that Immunobiology teaches

that "the Fc fragment of an antibody is a fragment that can be produced by enzymatic cleavage of the antibody molecule and contains the constant region of the antibody which does not bind the antigen."

Applicant respectfully disagrees that Immunobiology anticipates Claim 25. Claim 25 has been amended to clarify that the claimed antibody fragment specifically binds PRO347, the polypeptide of SEQ ID NO:50. According to MPEP § 2131, "a claim is anticipated only if each and every element, as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of CA*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The *identical* invention must be shown in as complete detail as contained in the . . . claim." *Id.* Also, see MPEP § 2131. Immunobiology does not describe, either expressly or inherently, binding to the polypeptide of SEQ ID NO:50 and therefore cannot anticipate Claim 25. Applicant respectfully requests that this ground of rejection be withdrawn.

Claims 22-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Botstein *et al.*, WO 99/35170, published July 15, 1999. Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, before Botstein *et al.* was published. Therefore, this ground of rejection has been obviated and Applicant respectfully requests that it be withdrawn. Applicant also notes that Botstein *et al.* is a Genentech application, filed the same day as provisional application 60/113,296, to which Applicant has demonstrated it is entitled to priority. Applicant further notes that the priority application, 60/113,296, has the same specification as the reference cited by the Examiner, Botstein *et al.*

Claims 22-27 are further rejected under 35 U.S.C. 102(b) as being anticipated by Holtzman, WO 99/54343, published October 28, 1999. As discussed above, Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, also before Holtzman was published. Therefore, this ground of rejection has also been obviated and Applicant respectfully requests that it be withdrawn.

### SUMMARY

Applicant believes that currently pending Claims 22-26 are patentable. Applicant respectfully requests the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

A handwritten signature in black ink, reading "C. Noel Kaman", written over a horizontal line.

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